EFFICIENT MODEL DRIVEN DESIGN OF CELL BASED PRODUCT MANUFACTURING

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Advanced Therapy Medicinal Products (ATMPs) pose a continuing challenge to manufacturing process development. Despite the adoption of a structured approach to development through systematic frameworks such as Quality by Design, a costly rate of process failure or underperformance is encountered at key transitions such as transfer to contract manufacture organizations or changes of scale or equipment. The complexity of the products, particularly the cell culture step, is frequently a contributor to such issues; this complexity challenges many process development tools, in particular the number of potential process variables and consequences results in a lower quality of evidence base informing early risk assessments, creates difficulties in experimental prioritization and efficiency, and can result in poor experimental coherence over the course of product development (i.e. a failure to efficiently harness/record all data and apply to manufacturing goals). We have proposed that rooting development in a suitable process model would lessen these issues. We have developed a framework that takes advantage of the commonality across ATMP manufacturing processes[(1)]. For example, features such as cell growth, paracrine inhibition or lineage selection, and cell death are representable by a limited set of mathematical building blocks. These behaviors interact with process operation to determine critical manufacturing outcomes such as product cost and identity. From an operational perspective there are a limited number of common process operations such as dilutions, purification or factor additions. This enables a modelling framework that can be constrained whilst still representing a wide range of process dynamic hypotheses and associated manufacturing scenarios. Case studies will be presented across a variety of platforms. These include intensification of hematopoietic lineage cell processing in suspension bioreactors (ambr15) including erythroblast and T-cell processing. In each of these cases a model of cell population growth was developed to optimize short term cell volume productivity. This was applied over a longer timeframe to quantify risks (on yield and phenotypic selection) of longer term operational strategies and control such as feed rates or variability in timings and volumes. This provides a basis to specify manufacture based on cost targets, operational constraints (e.g. feed frequency, reactor size) and risk tolerance. We will further present application of the same approach to gain insight into optimization of specific culture phenomena, such as lag phase and growth factor delivery, that have a potentially high impact on manufacturing outcomes.

(1) AJ Stacey, EA Cheeseman, KE Glen, RLL Moore, RJ Thomas. Experimentally integrated dynamic modelling for intuitive optimization of cell-based processes and manufacture. Biochem Eng J. 2018. 132: 130-138